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Pharmacotherapy

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DESCRIPTION

There are many compelling findings to suggest that a number of key psychobiological systems are dysregulated in PTSD patients. The strongest evidence shows alteration of adrenergic and hypothalamic–pituitary–adrenocorticol (HPA) mechanisms, heightened physiological reactivity, and sleep disturbances. PTSD-related abnormalities have also been detected or inferred about the serotonin, opioid, dopamine, thyroid, corticotropin releasing factor (CRF) and glutamatergic systems. Finally, the very frequent comorbidity with pharmacologically responsive disorders (e.g., major depression, panic) makes pharmacotherapy an important treatment option to be considered in most cases of PTSD.

Despite these scientific findings, pharmacotherapy for PTSD has primarily been guided by empirical evidence that a specific drug has efficacy against a specific symptom. Indeed, at present, very few data in all psychiatric disorders, including PTSD, link psychobiological abnormalities to specific drug effects. In research (and in clinical practice), almost every class of psychotropic agent has been prescribed for PTSD patients. Most studies involve antidepressants: selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and other serotonergic agents (trazodone and nefazodone). Antiadrenergic drugs tested include alpha-2 receptor agonists (clonidine and guanfacine) and the beta-

receptor antagonist (propranolol). Tests of mood-stabilizing anticonvulsants (carbamazepine and valproate) were initially based on a rationale related to their antikindling properties. Other drugs tested include benzodiazepine, anxiolytics, and antipsychotic agents.

GENERAL STRENGTH OF THE EVIDENCE

The strength of the evidence is best for the different classes of antidepressant agents that have been tested in most of the randomized clinical trials on pharmacotherapy. Clinical trials without randomization or controls have been carried out on antidepressants, antiadrenergic agents, anticonvulsants, and benzodiazepines. The only evidence for other drugs is based mostly on anecdotal observations and case reports.

COURSE OF TREATMENT

Earlier research findings suggest that controlled drug trials in PTSD should last at least 8–12 weeks, because shorter trials, generally, had been ineffective. More recent and much larger scale studies (with SSRIs) have raised questions about this belief, since clinically significant PTSD symptom reduction has been observed within 2–5 weeks. This clearly is a question requiring further research.

RECOMMENDATIONS

The strength of evidence for each recommendation is indicated in parentheses (i.e., AHCPR Levels A–F). The data on which these recommendations are based can be found in Tables 5.2–5.4 in Chapter 5.

1. *SSRIs (sertraline—Level A; fluoxetine—Level A/B; paroxetine, fluvoxamine—Level B).* SSRIs can be recommended as a first-line treatment for PTSD in nonveterans. They not only reduce DSM-IV PTSD symptoms and produce global improvement but also are effective against comorbid disorders and associated symptoms. Evidence from large, positive, double-blind trials has led to recent FDA approval for sertraline as an indicated treatment for PTSD. Therefore, it is given a full AHCPR Level A rating. Since there has only been one small, randomized clinical trial with fluoxetine published in a peer-reviewed journal, the level of evidence for fluoxetine (in Table 5.4) can only be considered an AHCPR Level A/B at this time. SSRIs have fewer side effects and greater safety than other antidepressants but may produce insomnia, agitation, gastrointestinal symptoms, and sexual dysfunction. Results

with veterans are difficult to interpret because of the severity and chronicity of PTSD in the veteran cohorts that have been tested thus far.

2. *MAOIs (phenelzine—Level A/B; moclobemide—Level B).* MAOIs have been shown to be effective for B symptoms and global improvement, with some efficacy against C symptoms; however, they have not been tested extensively. They are also effective antidepressants and antipanic agents. Of the two published, randomized clinical trials with phenelzine, one has serious methodological flaws. Therefore, the level of evidence supporting efficacy of this drug can only be Level A/B (see Table 5.4) pending further studies. Compliance with dietary restrictions is an important limitation of MAOI treatment. Furthermore, they are contraindicated in patients likely to use alcohol, illicit drugs, or certain drugs prescribed for other clinical conditions. Cardiovascular, hepatotoxic, and other side effects also must be monitored with MAOIs. If the reversible MAO-A inhibitor moclobemide proves safe and efficacious in future trials, it certainly will advance the argument that MAOIs should be considered first-line drugs for PTSD in the future.

3. *TCAs (imipramine/amitriptyline/desipramine—Level A).* TCAs have a similar spectrum of action (e.g., reduction of B symptoms and global improvement) as MAOIs but are less effective. Although they have fewer serious side effects than MAOIs, they may produce hypotension, cardiac arrhythmias, anticholinergic side effects, sedation, and arousal.

4. *Antiadrenergic agents (clonidine/guanfacine/propranolol—Level C).* Antiadrenergic agents appear to reduce arousal, reexperiencing, and possibly dissociative symptoms but have not been tested adequately in clinical trials. They are generally safe, although blood pressure and pulse rate must be monitored routinely. Special caution must be observed when prescribing these agents for patients with low blood pressure or those who receive antihypertensive medications. A few case reports suggest that tolerance is less likely to occur with guanfacine than with clonidine. Propranolol may sometimes produce depressive symptoms or psychomotor slowing.

5. *Anticonvulsants (carbamazepine/valproate—Level B).* These drugs have shown efficacy in reducing D symptoms (both drugs), B symptoms (carbamazepine only) and C symptoms (valproate only). They have been tested in several open clinical trials but not in any randomized clinical trials. Both drugs have proven efficacy in bipolar affective disorders, and both may cause significant side effects, especially carbamazepine.

6. *Benzodiazepines (alprazolam—Level B; clonazepam—Level C).* These are both effective anxiolytics and antipanic agents. Among PTSD patients, they produce their typical antiarousal effects without reducing either B or C symptoms. Discretion and caution should be exercised when considering their use for patients with past or present alcohol/drug abuse/dependency. They also may produce psychomotor slowing and exacerbate depressive symptoms. They do not appear to have any advantage over other classes of drugs and, therefore, cannot be recommended for use as monotherapy in

PTSD at this time. They may be beneficial as adjunctive treatment in time-limited treatment of disrupted sleep or for quick relief of global anxiety.

7. *Other serotonergic agents (nefazodone—Level B; trazodone—Level C; cyproheptadine/buspirone—Level F).* Open label trials with nefazodone indicate that it may improve sleep and reduce anger. Trazodone appears useful as an adjunct to SSRI treatment because it reverses SSRI-induced insomnia through a pharmacological mechanism of action that is synergistic with that of SSRIs. Since reports on the beneficial effects of both cyproheptadine and buspirone are anecdotal, there is no basis for recommending either drug at this time.

8. *Antipsychotics (thioridazine/clozapine/risperidone—Level F).* These drugs cannot be recommended for routine use in PTSD because only a few clinical anecdotes indicating their effectiveness have been published. They may ultimately prove to have a unique role for patients who are refractory to first- and second-line drugs—especially when these patients exhibit extreme hypervigilance, paranoid symptoms, agitation, or psychosis. They have many side effects, some of which are serious.

SUMMARY

The best evidence supports the use of SSRIs as first-line drugs for PTSD. There is also good evidence suggesting that MAOIs are moderately, and TCAs mildly effective agents, although both may produce adverse side effects. Evidence supporting the use of antiadrenergic and anticonvulsants agents is weak, not because of negative findings, but because there have been no randomized trials with either class of drugs. There is evidence to suggest that benzodiazepines are not useful for treating PTSD B or C symptoms. Finally, antipsychotic agents cannot be recommended for routine use, because only a few case reports have appeared in the literature.